General

Guideline Title

Tocilizumab for the treatment of rheumatoid arthritis (rapid review of technology appraisal guidance 198).

Bibliographic Source(s)

National Institute for Health and Clinical Excellence (NICE). Tocilizumab for the treatment of rheumatoid arthritis. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012 Feb. 55 p. (Technology appraisal guidance; no. 247).

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: National Institute for Health and Clinical Excellence (NICE). Tocilizumab for the treatment of rheumatoid arthritis. London (UK): National Institute for Health and Clinical Excellence (NICE); 2010 Aug. 50 p. (Technology appraisal guidance; no. 198).

Recommendations

Major Recommendations

This guidance replaces National Institute of Health and Clinical Excellence (NICE) technology appraisal guidance 198 issued in August 2010.

Tocilizumab, in combination with methotrexate, is recommended as an option for the treatment of rheumatoid arthritis in adults if:

- The disease has responded inadequately to disease-modifying anti-rheumatic drugs (DMARDs) and it is used as described for tumour necrosis factor (TNF) inhibitor treatments in Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis (NICE technology appraisal guidance 130), specifically the recommendations on disease activity and choice of treatment or
- The disease has responded inadequately to DMARDs and a TNF inhibitor and the person cannot receive rituximab because of a contraindication to rituximab, or because rituximab is withdrawn because of an adverse event, and tocilizumab is used as described for TNF inhibitor treatments in Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor specifically the recommendations on disease activity or
- The disease has responded inadequately to one or more TNF inhibitor treatments and to rituximab and
- The manufacturer provides tocilizumab with the discount agreed as part of the patient access scheme.

People currently receiving tocilizumab for the treatment of rheumatoid arthritis who do not meet the criteria described above should have the option to continue treatment until they and their clinicians consider it appropriate to stop.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Rheumatoid arthritis

Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

Clinical Specialty

Family Practice

Internal Medicine

Rheumatology

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To evaluate the clinical effectiveness and cost-effectiveness of tocilizumab for the treatment of rheumatoid arthritis

Target Population

Patients in England and Wales with moderate to severe active rheumatoid arthritis whose rheumatoid arthritis has responded inadequately to one or more disease modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor alpha (TNF-α) inhibitors and whose rheumatoid arthritis has responded inadequately to rituximab, or in whom rituximab is not tolerated or is contraindicated

Interventions and Practices Considered

Tocilizumab in combination with methotrexate

Major Outcomes Considered

- Clinical effectiveness

- American College of Rheumatology (ACR) scores
- Disease Activity Scores (DAS)
- European League Against Rheumatism (EULAR) scores
- Health Assessment Questionnaire (HAQ) score
- Fatigue (FACIT-F) score
- Short Form (SF-36) scores
- The Sharp radiographic assessment scores
- Adverse events

- Cost-effectiveness

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The ERG report for technology appraisal 198 was prepared by West Midlands Health Technology Assessment Collaboration, University of Birmingham. The Decision Support Unit (DSU) report for TA198 *Tocilizumab for the treatment of rheumatoid arthritis* was prepared by the Centre for Health Economics, University of York. The DSU report for this appraisal, TA247 *Rheumatoid arthritis – tocilizumab (rapid review TA198)*, was prepared by the School of Health and Related Research, University of Sheffield. (See the "Availability of Companion Documents" field.)

Clinical Effectiveness

Description of Manufacturer's Search Strategy and Comment on Whether the Search Strategy Was Appropriate

Summary from the Manufacturer's Submission

The following sources were searched between 20th and 21st January 2009: MEDLINE 1993 to date (MEYY), Medline In Process latest eight weeks (MEIP), EMBASE 1993 to date (EMYY), EMBASE latest eight weeks (EMBA), Cochrane Library, EULAR abstracts (European League Against Rheumatism) 2002-2008, ACR (American College of Rheumatology) abstracts 2002-2008. Internal study reports and regulatory submission documents were accessed through company databases.

The searches were limited to humans and clinical trials. Data from clinical studies conducted in Japan by Chugai were not included as data in this patient population was not considered relevant to European patients.

Despite the limitations of the searches, those done by the ERG of MEDLINE, EMBASE and Cochrane Library (see Appendix 1 of the ERG report [see the "Availability of Companion Documents" field]) verified that all relevant published studies were identified.

For additional ERG comments regarding the manufacturer's search strategy, refer to Section 4 of the ERG report.

Statement of the Inclusion/Exclusion Criteria Used in the Study Selection and Comment on Whether They Were Appropriate

The stated inclusion and exclusion criteria were very unclear:

Inclusion Criteria

Published papers or abstracts which evaluated the following were included:

- Tocilizumab (or atlizumab prior to 2005) was the major focus of the paper.
- Rheumatoid arthritis was a major focus of the paper.
- Patient population consisted of patients who had responded inadequately or who were intolerant to one or more disease-modifying anti-

rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists, to be consistent with the European Union (EU) licence for tocilizumab, including dose
- Controlled clinical studies
- Documents relating to humans

Exclusion Criteria

Published papers or abstracts which evaluated the following were excluded:

- Any papers providing a review, update or commentary on data published elsewhere were excluded.
- Any papers which only mentioned tocilizumab within a discussion of treatments for rheumatoid arthritis were excluded.
- Papers covering the use of tocilizumab in Castleman's disease, juvenile idiopathic arthritis, other autoimmune diseases or other off-licence indications were excluded.
- Clinical studies conducted in Japanese patients were not included, as data generated in this patient population was not considered sufficiently relevant to European patients.
- Animal studies or in vitro research
- Case reports

Economic Evaluation

Description of Manufacturer's Search Strategy and Comment

Summary from the Manufacturer's Submission

The review updated and extended the searches in the review by Chen et al., 2006. This review was included as were 10 already identified studies from the report.

Two search strategies (see Appendices 5 and 6 in the ERG; see the "Availability of Companion Documents" field) from the review by Chen et al., 2006 were combined and adapted for use in: MEDLINE, EMBASE, MEDLINE In Process, Health Technology Assessment (HTA) database (Cochrane Library 2008 Issue 4), National Health Service Economic Evaluation Database (NHS EED) (Cochrane Library 2008 Issue 4) and Health Economic Evaluation Database (HEED) between 24th December 2008 and 6th January 2009.

Only articles in English were included.

Searches for Adalimumab, Etanercept and Infliximab were limited to 2005 onwards; no time limits were applied to searches for the other interventions (Abatacept, Golimumab, Certolizumab Pegol, and Rituximab).

Comment

The searches were sound overall and were unlikely to have missed relevant studies.

Number of Source Documents

Clinical Effectiveness

There were three groups of included studies:

- Five randomised controlled trials (RCTs) discussed in the clinical effectiveness section of the Evidence Review Group (ERG) report (see the "Availability of Companion Documents" field)
- Two long term single arm extension studies of tocilizumab
- Nineteen RCTs used in the mixed treatment comparison (MTC)

Cost-effectiveness

- No published cost-effectiveness studies were identified.
- The manufacturer submitted an economic model.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Meta-Analysis of Randomized Controlled Trials

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an Evidence Review Group (ERG) report. The ERG report for technology appraisal 198 was prepared by West Midlands Health Technology Assessment Collaboration, University of Birmingham. The Decision Support Unit (DSU) report for TA198 *Tocilizumab for the treatment of rheumatoid arthritis* was prepared by the Centre for Health Economics, University of York. The DSU report for this appraisal, TA247 *Rheumatoid arthritis – tocilizumab (rapid review TA198)*, was prepared by the School of Health and Related Research, University of Sheffield (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Description and Critique of Manufacturers Approach to Validity Assessment

Validity assessment was by the use of standard questions, and all five included trials were discussed together for each of the questions (see Section 4.1 of the ERG report for the list of questions).

The submission mentions long term follow up of five years, but the two 5-year follow-up studies have a single arm only with patients given tocilizumab. No comparator of placebo, conventional disease modifying anti-rheumatic drugs (DMARDs) or biologic agents will be available, so it is unclear how these 5-year studies can establish effectiveness. It is debatable whether follow-up in the five included studies (24 weeks) is adequate. It is not possible to tell whether any initial treatment effect wanes after time with this short length of follow-up.

Describe and Critique the Statistical Approach Used

The randomised controlled trials (RCTs) used standard approaches to statistical analyses. For individual RCT results, per protocol and intention-to-treat (ITT) analyses were available in the trial reports. Only the American College of Rheumatology (ACR)20, ACR50 and ACR70 results for Option (WA17822), Lithe (17823) and Toward (WA18063) RCTs were presented in the submission.

Critique of Submitted Evidence Syntheses

The meta-analysis was of three RCTs only – Option (WA17822), Lithe (WA17823) and Toward (WA18063) because the participants in these RCTs had an inadequate response to methotrexate (MTX) or DMARD. The comparator in the meta-analysis was placebo.

The meta-analysis result in the plot shown in the ERG report does not appear to be based on the adjusted odds ratios from the three trials as it looks to be too far to the left. Also the scale is not logarithmic. The axis in the submission plot is labelled odds ratio (OR) but zero and minus-one appear on the axis; minus-one is an impossible value for odds ratio and makes the plot confusing. These values are familiar for log odds ratio but it is clear that the confidence intervals (CIs) correspond to an OR rather than a log OR (i.e., they are not symmetrical about the point estimates). For a forest plot of OR to do this the x axis needs to be on a log scale. A plot of log OR would provide symmetrical CIs with the axis linear on a log OR scale.

The forest plot has been redrawn (see the ERG report) to include the unadjusted odds ratios reported for the studies.

It is unclear if or how the meta-analysis was used subsequently in the submission. The submission used ACR50 and ACR70 results as well as ACR20 scores to obtain Health Assessment Questionnaire (HAQ) values and thence utility estimates to feed the economic model. However no meta-analyses of these outcomes were presented.

Refer to Section 4 of the ERG report (see the "Availability of Companion Documents" field) for additional information.

In addition to the original submission, the manufacturer of tocilizumab provided updated data with a maximum of 180 weeks of follow-up. The response rates of all people who received at least one dose of tocilizumab in the OPTION, AMBITION, RADIATE and TOWARD trials were analysed. A total of 3986 people were included in the long-term analyses.

Economic Evaluation

Overview of Manufacturer's Economic Evaluation

As there were no United Kingdom (UK)-based economic evaluations of tocilizumab, the manufacturer conducted a *de novo* economic model. Table 6 of the ERG report summarises the key features of the model.

Populations

Two patient cohorts were considered, consistent with the licensed indication of tocilizumab:

- Moderate to severe rheumatoid arthritis (RA) patients who have had an inadequate response to one or more traditional DMARDs.
- Moderate to severe RA patients who have had an inadequate response to one or more anti-tumour necrosis factor (TNF)-α agents.

It should be noted that no subgroup analysis of patients intolerant to methotrexate (MTX) was conducted, even though these patients are specifically mentioned in the scope. The submission assumes that tocilizumab will be administered together with MTX, so the submission has not shown any evidence of cost-effectiveness in a MTX-intolerant population.

Perspective and Time Horizon

Costs were considered from a National Health Service (NHS) and Personal Social Services perspective (in practice NHS only), consistent with the NICE reference case. A time horizon over a patient lifetime was applied, as is appropriate for a chronic disease.

Model Validation

Refer to Section 5.1 of the ERG report for information on model validation.

Critique of Approach Used

A summary of the model and critical appraisal of its features can be found in Appendix 3 of the ERG report.

Refer to Section 5 of the ERG report (see the "Availability of Companion Documents" field) for additional information on the economic analysis.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Clinical Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document' (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE website. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who Is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

The manufacturer did not identify any economic evaluations of tocilizumab and developed an economic model for the submission. This was an individual sampling model with a hypothetical homogenous cohort. The model used a lifetime horizon for costs and benefits. The manufacturer's initial economic model compared a treatment sequence that included tocilizumab with the same treatment sequence without tocilizumab for two populations. For the DMARD-IR population (people whose rheumatoid arthritis had responded inadequately to previous disease modifying anti-rheumatic drugs [DMARDs] but before treatment with a tumour necrosis factor alpha [TNF-α] inhibitor), tocilizumab plus methotrexate was the first biological treatment and if the condition did not respond or if the American College of Rheumatology (ACR)20 response rate was no longer achieved then etanercept plus methotrexate was the next treatment. This was followed by rituximab plus methotrexate, then leflunomide, then gold, then ciclosporin until people withdrew from the last treatment (ciclosporin) and moved on to palliative care. The sequence was the same for the comparator arm, but excluded tocilizumab plus methotrexate at the beginning. For the TNF-IR population (people whose rheumatoid arthritis had responded inadequately to previous TNF-α inhibitors but before treatment with rituximab), the sequence was the same as the DMARD-IR population, except for the omission of etanercept plus methotrexate (that is, the first treatment in the comparator arm was rituximab plus methotrexate).

For the DMARD-IR population, the treatment sequence including tocilizumab plus methotrexate compared with the sequence without tocilizumab produced incremental costs of £23,253 and incremental quality-adjusted life years (QALYs) of 1.17. This resulted in a base-case incremental cost-effectiveness ratio (ICER) of £19,870 per QALY gained. For the TNF-IR population, the treatment sequence including tocilizumab plus methotrexate compared with the sequence without tocilizumab produced incremental costs of £26,640 and incremental QALYs of 1.21. This resulted in a base-case ICER of £22,003 per QALY gained. Probabilistic sensitivity analyses suggested that the addition of tocilizumab and methotrexate to the treatment sequences had a 56.4% and 22.4% probability of being cost effective (for the DMARD-IR and TNF-IR populations respectively) if the maximum acceptable amount to pay for a QALY gained is £20,000. All scenario analyses presented by the manufacturer resulted in ICERs of less than £30,000 per QALY gained. The ICERs increased to £24,905 and £24,739 per QALY gained for the DMARD-IR and TNF-IR populations respectively, using an assumption of no change in Health Assessment Questionnaire (HAQ) score (that is, no continued improvement on tocilizumab after the initial ACR response).

In response to three rounds of consultation for the original guidance on tocilizumab for rheumatoid arthritis (National Institute for Clinical Excellence and Health [NICE] technology appraisal guidance 198), the manufacturer presented revised ICERs for the DMARD-IR and TNF-IR populations incorporating some of the Evidence Review Group's (ERG's) suggested changes. The manufacturer's revised ICER for the DMARD-IR population increased from £19,870 to £21,733 per QALY gained, and increased from £22,003 to £23,285 per QALY gained for the TNF-IR population. The ICER for tocilizumab used after rituximab was £23,735 per QALY gained. The ICER for tocilizumab for people who are

intolerant to rituximab or for whom rituximab is contraindicated was £20,242 per QALY gained.

Decision Support Unit Report 2010

In 2010, the Decision Support Unit (DSU) was asked to undertake additional cost-effectiveness analyses to validate the manufacturer's ICERs submitted after the third round of consultation, and to conduct sensitivity analyses to address the Appraisal Committee's concerns about key parameter assumptions. Using the threshold for cost-effectiveness (£30,000 per QALY gained), the results of the fully incremental analysis undertaken by the DSU in the 2010 report indicated that using tocilizumab as a first-line treatment before etanercept would not be cost effective for any approach and with any set of parameter assumptions (including the manufacturer's base-case assumptions). Using tocilizumab as a second-line treatment before rituximab would only be cost effective if it is assumed that tocilizumab has long-term HAQ improvement and there is no HAQ improvement assumed with other biological treatments. However, if tocilizumab has zero HAQ improvement, then tocilizumab would only be cost effective when used as a third-line treatment after rituximab. If tocilizumab has zero HAQ improvement and the administration costs of tocilizumab are doubled, then tocilizumab is never cost effective (that is, standard care is the most cost-effective sequence). For patients who have an intolerance to rituximab, or for whom rituximab is contraindicated, adding tocilizumab to the current standard care is cost effective. However, if tocilizumab does not have a different effect on long-term HAQ and the administration costs of tocilizumab are doubled, then the current standard care would be more cost effective for this population.

Decision Support Unit Report 2011

In 2011, the DSU was asked to undertake a review of whether the manufacturer had correctly implemented the Department of Health approved patient access scheme within their cost-effectiveness analysis. Additionally the DSU critiqued the changes to the costs of tocilizumab and ensured the Committee's agreed assumptions from the guidance on tocilizumab for rheumatoid arthritis (NICE technology appraisal guidance 198) had been used as the starting point within the economic analysis.

The DSU reported the results of their exploratory analysis for the DMARD-IR population, which included the same treatment sequences in an incremental analysis as those modelled by the manufacturer. All ICERs incorporated the discount for tocilizumab agreed as part of the patient access scheme. In this analysis, three sequences were extendedly dominated (first: etanercept followed by rituximab; second: tocilizumab as the first treatment; third: tocilizumab as the second treatment). The ICER for tocilizumab as the third treatment in the sequence was £28,380 per QALY gained compared with £8134 per QALY gained from the manufacturer's analysis.

The DSU reported the results of their exploratory analysis for the TNF-IR population, which included the same treatment sequences in an incremental analysis as those modelled by the manufacturer. All ICERs incorporated the discount for tocilizumab agreed as part of the patient access scheme. In this analysis, tocilizumab followed by rituximab was dominated (was less effective than and at least as costly) by rituximab followed by tocilizumab. The ICER for rituximab followed by tocilizumab was £18,527 per QALY gained compared with the manufacturer's estimate of £22,690 per QALY gained.

Summary of Appraisal Committee's Key Conclusions

The manufacturer's analysis had not taken into account extended dominance and that this had an impact on the ICERs. The Committee concluded that the DSU's 2011 exploratory analyses should be used as the basis for determining the cost-effectiveness of tocilizumab.

Incorporation of Health-Related Quality-of-Life Benefits and Utility Values

The Committee noted that the manufacturer's mapping of HAQ scores to European quality of life health-state questionnaire (EQ-5D) utility values resulted in negative utility values. The Committee heard from the manufacturer that it was possible that there were some people with rheumatoid arthritis who may experience negative utility values. The Committee therefore accepted that the calculation of some ICERs would include negative utility values but concluded that this was acceptable because of the low impact on the ICERs.

Are There Specific Groups of People for Whom the Technology Is Particularly Cost Effective?

The Committee heard from the manufacturer that it was seeking a recommendation for tocilizumab as an option along with other biological treatments in the treatment pathway. It therefore considered that there were four possible scenarios for including tocilizumab in the treatment pathway:

- Tocilizumab after two DMARDs as an alternative to TNF-α inhibitors
- Tocilizumab after TNF-α inhibitors as an alternative to rituximab
- Tocilizumab after TNF-α inhibitors when a person is intolerant to rituximab or for whom rituximab is contraindicated
- Tocilizumab as an addition to the treatment pathway after rituximab

What Are the Key Drivers of Cost-effectiveness?

The Committee concluded that the improved cost-effectiveness of tocilizumab as the first biological treatment compared with etanercept was due to the cost of time on treatment, rather than any substantial differences in clinical or cost-effectiveness between tocilizumab and etanercept.

Most Likely Cost-effectiveness Estimate (Given as an ICER)

For the DMARD-IR population: three sequences were extendedly dominated (less effective than and at least as costly as a combination of other drug sequences). When tocilizumab is the third biological in the sequence the most plausible estimate of the ICER is £28,400 per QALY gained. The Committee accepted that some uncertainty around the point estimates of the ICERs was likely.

For the TNF-IR population: the Committee accepted the ICER of £18,500 per QALY gained as the most plausible ICER estimate for tocilizumab following rituximab in this population.

For the DMARD-IR rituximab intolerant population: the Committee noted that the most plausible estimate for the ICER ranged from £10,700 per QALY gained for the sequence in which etanercept followed tocilizumab to £30,100 per QALY gained in the sequence where tocilizumab followed etanercept.

Refer to Sections 3 and 4 of the original guideline document for details of the economic analyses provided by the manufacturer, the Evidence Review Group's (ERG) comments, the DSU report, and the Appraisal Committee considerations.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

Consultee organisations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

The Appraisal Committee considered clinical and cost-effectiveness evidence submitted by the manufacturer of tocilizumab, a review of this submission by the Evidence Review Group (ERG), and additional analyses by the Decision Support Unit. The main clinical effectiveness evidence came from randomised controlled trials. For cost-effectiveness, the Appraisal Committee considered an economic model submitted by the manufacturer.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate use of tocilizumab for the treatment of rheumatoid arthritis

Potential Harms

- The summary of product characteristics (SPC) lists the following as the most commonly reported adverse drug reactions associated with tocilizumab treatment: upper respiratory tract infections, nasopharyngitis, headache, hypertension, and increased alanine transaminase.
- The manufacturer reported that adverse events associated with the mechanism of interleukine-6 receptor (IL-6R) inhibition were observed in all tocilizumab treatment groups. These adverse events included transient hepatic transaminase elevations, asymptomatic elevations of indirect bilirubin, transient neutropenia, and lipid elevations that appear to occur in association with marked decreases in acute phase proteins. In addition, serious infections associated with the immunomodulatory effects of tocilizumab were comparable with the incidence of serious infections with tumour necrosis factor (TNF)-α inhibitors.
- Adverse events reported more frequently with tocilizumab 8 mg/kg monotherapy than in the methotrexate group were abdominal pain and discomfort, headache, dizziness, rash, pruritis and elevated blood pressure, neutropenia, leukopenia and hyperlipidaemia. Most of these events were mild and transient.

For full details of side effects and contraindications, see the SPC.

Contraindications

Contraindications

Tocilizumab is contraindicated in people with active, severe infections.

For full details of side effects and contraindications, see the summary of product characteristics (SPC).

Qualifying Statements

Qualifying Statements

- This guidance represents the view of the National Institute for Health and Clinical Excellence (NICE) and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

Implementation of the Guideline

Description of Implementation Strategy

- The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the National Health Service (NHS) in England and Wales on implementing National Institute for Health and Clinical Excellence (NICE) technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. When there is no NICE technology appraisal guidance on a drug, treatment or other technology, decisions on funding should be made locally.
- The Department of Health and the manufacturer have agreed that tocilizumab will be available to the NHS with a patient access scheme in which a discount from the list price is applied to original invoices. The level of the discount is commercial in confidence. It is the responsibility of the manufacturer to communicate the level of discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to the manufacturer customer care (0800 731 5711).

- NICE has developed tools to help organisations put this guidance into practice (listed below). These are available on the NICE website (http://guidance.nice.org.uk/TA247).
  - A costing statement explaining the resource impact of this guidance

Implementation Tools

Foreign Language Translations

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

National Institute for Health and Clinical Excellence (NICE). Tocilizumab for the treatment of rheumatoid arthritis. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012 Feb. 55 p. (Technology appraisal guidance; no. 247).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2010 Aug (revised 2012 Feb)

Guideline Developer(s)

National Institute for Health and Care Excellence (NICE) - National Government Agency [Non-U.S.]

Source(s) of Funding

National Institute for Health and Clinical Excellence (NICE)

Guideline Committee

Appraisal Committee

Composition of Group That Authored the Guideline

Committee Members: Professor Kathryn Abel, Reader and Consultant Psychiatrist/Director of Centre for Women's Mental Health, University of Manchester; Dr David Black, Director of Public Health, Derbyshire County Primary Care Trust; Dr Daniele Bryden, Consultant in Intensive Care Medicine and Anaesthesia, Sheffield Teaching Hospitals NHS Trust; Dr Andrew Burnett, Director for Health Improvement and Medical Director, NHS Barnet, London; David Chandler, Lay member; Dr Mary Cooke, Lecturer, School of Nursing, Midwifery and Social Work, University of Manchester; Dr Chris Cooper, General Practitioner, St John's Way Medical Centre, London; Dr Christine Davey, Research Adviser, North and East Yorkshire Alliance Research and Development Unit, York; Richard Devereaux-Phillips, Director, Public Policy and Advocacy NW Europe, BD, Oxford; Professor Rachel A Elliott, Lord Trent Professor of Medicines and Health, University of Nottingham; Dr Alan Haycox, Reader in Health Economics, University of Liverpool Management School; Professor Cathy Jackson, Professor of Primary Care Medicine, University of St Andrews; Dr Peter Jackson, Clinical Pharmacologist, University of Sheffield; Dr Janice Kohler, Senior Lecturer and Consultant in Pediatric Oncology, Southampton University Hospital Trust; Henry Marsh, Consultant Neurosurgeon, St George's Hospital, London; Professor Gary McVeigh, Professor of Cardiovascular Medicine, Queen's University Belfast and Consultant Physician, Belfast City Hospital; Professor Eugene Milne, Deputy Regional Director of Public Health, North East Strategic Health Authority, Newcastle upon Tyne; Dr Neil Myers, General Practitioner, Glasgow; Professor Stephen O'Brien, Professor of Haematology, Newcastle University; Dr Danielle Preedy, Lay member; Dr Peter Selby, Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust; Dr Surinder Sethi, Consultant in Public Health Medicine, North West Specialised Services Commissioning Team, Warrington; Professor Andrew Stevens, Chair of Appraisal Committee C, Professor of Public Health, University of Birmingham; Dr Matt Stevenson, Technical Director, School of Health and Related Research, University of Sheffield; Professor Paul Trueman, Professor of Health Economics, Brunel University, London; Dr Judith Wardle, Lay member

Financial Disclosures/Conflicts of Interest

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: National Institute for Health and Clinical Excellence (NICE). Tocilizumab for the treatment of rheumatoid arthritis. London (UK): National Institute for Health and Clinical Excellence (NICE); 2010 Aug. 50 p. (Technology appraisal guidance; no. 198).

Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site .

Availability of Companion Documents

The following are available:

- Tocilizumab for the treatment of rheumatoid arthritis (review of NICE technology appraisal guidance 198). Costing statement. London

(UK): National Institute for Health and Clinical Excellence (NICE); 2012. 4 p. (Technology appraisal 247). Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site .

- Tocilizumab for the treatment of rheumatoid arthritis. Evidence review group report. West Midlands Health Technology Assessment Collaboration. University of Birmingham; 2009 Oct. 99 p. (Technology appraisal 198). Electronic copies: Available in PDF from the NICE Web site .
- Tocilizumab for the treatment of rheumatoid arthritis. Report by the Decision Support Unit. Centre for Health Economics, University of York; 2010 May 6. 30 p. Electronic copies: Available in PDF from the NICE Web site .
- Tocilizumab for the treatment of rheumatoid arthritis. Report by the Decision Support Unit. School of Health and Related Research, University of Sheffield; 2011 Sep 2. 29 p. Electronic copies: Available in PDF from the NICE Web site .

Patient Resources

The following is available:

- Tocilizumab for the treatment of rheumatoid arthritis. Understanding NICE guidance. Information for people who use NHS services. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012 Feb. (Technology appraisal 247). Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site . Also available in Welsh from the NICE Web site .

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